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Effects of Androgenic-Anabolic Steroids in Athletes

Fred Hartgens[1] and *Harm Kuipers*[2]

1 Department of Surgery, Outpatient Clinic Sports Medicine, University Hospital Maastricht, and Sports Medicine Center Maastricht, Maastricht, The Netherlands
2 Department of Movement Sciences, Maastricht University, Maastricht, The Netherlands

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Abstract

Androgenic-anabolic steroids (AAS) are synthetic derivatives of the male hormone testosterone. They can exert strong effects on the human body that may be beneficial for athletic performance. A review of the literature revealed that most laboratory studies did not investigate the actual doses of AAS currently abused in the field. Therefore, those studies may not reflect the actual (adverse) effects of steroids. The available scientific literature describes that short-term administration of these drugs by athletes can increase strength and bodyweight. Strength gains of about 5–20% of the initial strength and increments of 2–5kg bodyweight, that may be attributed to an increase of the lean body mass, have been observed. A reduction of fat mass does not seem to occur. Although AAS administration may affect erythropoiesis and blood haemoglobin concentrations, no effect on endurance performance was observed. Little data about the effects of AAS on metabolic responses during exercise training and recovery are available and, therefore, do not allow firm conclusions.

The main untoward effects of short- and long-term AAS abuse that male athletes most often self-report are an increase in sexual drive, the occurrence of acne vulgaris, increased body hair and increment of aggressive behaviour. AAS administration will disturb the regular endogenous production of testosterone and gonadotrophins that may persist for months after drug withdrawal. Cardiovascular risk factors may undergo deleterious alterations, including elevation of blood pressure and depression of serum high-density lipoprotein (HDL)-, HDL2- and HDL3-cholesterol levels. In echocardiographic studies in male athletes, AAS did not seem to affect cardiac structure and function, although in animal studies these drugs have been observed to exert hazardous effects on heart structure and function. In studies of athletes, AAS were not found to damage the liver. Psyche and behaviour seem to be strongly affected by AAS. Generally, AAS seem to induce increments of aggression and hostility. Mood disturbances (e.g. depression, [hypo-]mania, psychotic features) are likely to be dose and drug dependent.

AAS dependence or withdrawal effects (such as depression) seem to occur only in a small number of AAS users. Dissatisfaction with the body and low self-esteem may lead to the so-called 'reverse anorexia syndrome' that predisposes to the start of AAS use. Many other adverse effects have been associated with AAS misuse, including disturbance of endocrine and immune function, alterations of sebaceous system and skin, changes of haemostatic system and urogenital tract. One has to keep in mind that the scientific data may underestimate the actual untoward effects because of the relatively low doses administered in those studies, since they do not approximate doses used by illicit steroid users.

The mechanism of action of AAS may differ between compounds because of variations in the steroid molecule and affinity to androgen receptors. Several pathways of action have been recognised. The enzyme 5-α-reductase seems to play an important role by converting AAS into dihydrotestosterone (androstanolone) that acts in the cell nucleus of target organs, such as male accessory glands, skin and prostate. Other mechanisms comprises mediation by the enzyme aromatase that converts AAS in female sex hormones (estradiol and estrone), antagonistic action to estrogens and a competitive antagonism to the glucocorticoid receptors. Furthermore, AAS stimulate erythropoietin synthesis and red cell production as well as bone formation but counteract bone breakdown. The effects on the cardiovascular system are proposed to be mediated by the occurrence of AAS-induced atherosclerosis (due to unfavourable influence on serum lipids and lipoproteins), thrombosis, vasospasm or direct injury to vessel walls, or may be ascribed to a combination of the different mechanisms. AAS-induced increment of muscle tissue can be attributed to hypertrophy and the formation of new muscle fibres, in which key roles are played by satellite cell number and ultrastructure, androgen receptors and myonuclei.

For many years, androgenic-anabolic steroids (AAS) have been popular among athletes both for performance improvement and for aesthetic reasons. The first documented reports of misuse of AAS by athletes stem from the 1950s. At the world championship weightlifting in Vienna (Austria) it was rumoured that the Russian team physician told the US team doctor that some Russian athletes used androgens to enhance their performance, and that back in the US the team physician introduced the administration of these drugs in athletes. Since the first results were less motivating, he concluded that androgens might exert particular psychological effects. However, since several AAS-using athletes won competitions and championships in that period, the abuse of these agents in sport began to spread.[1-3]

The International Olympic Committee (IOC) started the fight against doping in the 1960s. The first doping control procedures were performed at the Mexico Olympic Games in 1968 and AAS were placed on the list of banned substances in 1976. A decade later the IOC decided to introduce the so-called 'out-of-competition' doping controls. The reason for starting these controls was that many athletes used doping substances (especially AAS) in their training period rather than during competition. For many years the anabolic agents have been by far the most detected doping substances in IOC-accredited laboratories.[4]

Abuse of AAS is not limited to elite athletes, but is also common practice among many amateur and recreational athletes. It has been established that the use among athletes in gyms is extensive. Although the sports organisations and media pay less attention

to the abuse of AAS by these athletes it is of great medical concern. In recent years many reports on the side effects of these substances in athletes have been published.[5-13]

In this article we review the effects of AAS administration on body composition and performance as well as the untoward effects on health status in athletes. Furthermore, we describe what AAS are and discuss the mechanism of action of these steroids.

1. What Are Androgenic-Anabolic Steroids (AAS)?

AAS are synthetic derivatives of the male hormone testosterone. In humans, testosterone is produced in the Leydig cells in the testes. For many years it had been well known that castration resulted in the loss of certain secondary male sex characteristics; therefore, in the early 1900s several attempts were made to obtain a substance with the same potential as testosterone. At the end of the 1920s an active extract became available and the production of synthetic androgens was possible in 1935.[14-16] Although the separation of androgenic and anabolic properties was pursued, complete separation was not successful; however, there are now products available with more androgenic and substances with more anabolic properties. The androgenic actions primarily include the development of the male characteristics, that is, increased strength, voice deepening and the typical male hair growth. The anabolic action affects protein metabolism by stimulation of protein synthesis and inhibition of protein breakdown.[15,17]

Neither oral nor parenteral administration of exogenous testosterone exerts significant effects in the human body because they are rapidly metabolised. To circumvent this problem, several chemical modifications of testosterone have been developed. The variety of these modifications has led to substances with different action modes. Three major modifications can be distinguished that have therapeutic potential. First, alkylation at the 17-α-position with methyl or ethyl group. Alkylation was important to create orally active compounds since this implies slower degradation of the drug by the liver. Secondly, through esterification of testosterone and nortestosterone at the 17-β-position it was possible to administer these substances parenterally and the duration of effectiveness could be prolonged. Agents soluble in oily vehicles used for injections may be present in the body for several months. Finally, alterations of the ring structure of testosterone were applied for both oral and parenteral agents and increased the activity of these substances.[17,18]

Currently, the therapeutic use of AAS is limited and may vary between steroids. The most important indications are endocrine dysfunction of the testes and of the hypothalamus-pituitary-gonadal axis (i.e. male hypogonadism and growth retardation). Furthermore, AAS are used to treat disturbances of nitrogen balance and muscular development and several other non-endocrine diseases, including several forms of anaemia, hereditary angioneurotic oedema, breast carcinoma and osteoporosis.

In addition to the established indications, several attempts have been made to develop adequate treatment of male infertility with testosterone administration. Conversely, testosterone is also subject to extensive clinical trials in the development of a male contraceptive. To date, these efforts have not been satisfactory.[19-22]

Recently, the value of AAS treatment in several acute and chronic diseases has been investigated.[23] From clinical trials it seems likely that small amounts of AAS may exert a positive effect on nitrogen balance in polytrauma patients, after abdominal surgery and after burn injury.[23] Additionally, in chronic obstructive pulmonary disease[24,25] and HIV patients[26-29] AAS have been shown to increase lean body mass, although this effect seems to be related to nutritional status and intake.[23] Furthermore, clinical data indicate that these drugs may exert beneficial effects in muscular dystrophy[30] and several dermatological diseases.[31,32] However, because of the small number of investigations, the actual value of AAS treatment in these conditions has to be established.

2. Limitations of Research on the Effects of AAS in Athletes

Scientific research on the effects of AAS in athletes started in the 1960s. Since then, a number of studies have been published. The first studies focused on athletic performance, with special attention to strength and endurance capacity alterations. Later, in part along with the dramatic increase of AAS misuse by athletes for aesthetic purposes, the impact of AAS on body composition became of interest. Concurrent with the increased misuse of AAS for non-medical reasons, more attention was paid to the adverse effects. This led to an overwhelming number of publications with large methodological and qualitative differences. As a result, different conclusions and interpretations were drawn. Therefore, several methodological considerations need to be addressed.

2.1 Study Design

Although a lot of AAS studies have been published, only a few meet current scientific quality standards of randomised, double-blind placebo-controlled study design. Furthermore, the design needs to follow AAS abuse practices of real life to obtain insight into what really happens in sport. In investigating the effects of AAS, the combination of both demands conflicts, especially because of ethical considerations. It is not acceptable to expose healthy humans to potentially hazardous drugs in supratherapeutic dosages for the single purpose of improving sports performance. Therefore, different study designs have been used, with each possessing some benefits and disadvantages.

2.2 Cross-Sectional Studies

A number of cross-sectional studies have misinterpreted the observed differences between AAS users and controls by attributing them to a causal relationship. Cross-sectional studies are not designed to study causal relationships; at most, they are to observe an association. For example, several cross-sectional studies concluded that differences of heart morphology between AAS users and controls were attributed to AAS use.[33,34]

2.3 Prospective, Interventional Studies

Although scientifically preferable, randomised, placebo-controlled studies have several disadvantages for investigating AAS effects in athletes. Because of ethical considerations, only relatively low doses for a limited time period can be studied. However, such studies do not reflect sports practices and may therefore provide only a glimpse of actual effects.

2.4 Prospective, Observational Studies

Prospective, observational studies can overcome several limitations of interventional studies, but have the disadvantage of selection bias and are less controllable.

2.5 Long-Term Studies

To date, no studies investigating the long-term effects of AAS are available. Only a few observational reports describing alterations of body composition and health status in a single subject have been published. Therefore, the long-term effects of AAS abuse are as yet unknown.

2.6 Case Reports

Case reports are commonly used to describe the association of abuse of AAS with the most unexpected, severe and dramatic disease conditions. Such reports must be interpreted with caution. They are characterised by describing a possible relationship between AAS administration and the disease condition and, since evidence is lacking, may exaggerate the problem.

2.7 Subjects and Outcome Measures

Inclusion of athletes of only one sport discipline may improve validity of the observations since athletes from different sports have set different objectives to use AAS. For example, in a number of studies ‘strength athletes’ were the subjects of the investigation. ‘Strength athletes’ is a term compris-

ing athletes from several disciplines with different goals. A powerlifter's objective is to lift weights, whereas bodybuilders are focused to enlarge muscle mass and dimensions. In wrestlers, absolute power and muscle mass are not important at all. Studying a varsity group of so-called 'strength athletes' may influence study results of body composition, muscle mass and strength.

2.8 Regimens, Doses and Duration of AAS Use

Another problem researchers are confronted with is the regimens used by athletes, especially those involved in strength sports. Athletes use so-called stacking regimens, characterised by the administration of several AAS simultaneously in huge amounts in weekly changing dosages. Such regimens are applied based on the beliefs and insights of the athlete, although no rationale for such a regimen is available yet. Another problem is that since the substances are obtained from the black market quality is not guaranteed. This may also induce the ongoing increase of doses administered since many vials and tablets obtained on the black market only contain a fraction of the declared dosage.

2.9 Selection Bias

Because of ethical considerations, many studies chose to study volunteers who had decided to self-administer AAS and subjects who were not willing to take AAS at all. The inclusion of participants without the possibility of randomisation may influence the study outcome as a result of selection bias. To reduce this problem, strict inclusion and exclusion criteria have to be set, especially with respect to training and training history, as well to health status and risk factors of diseases.

2.10 Summary

In summary, it has to be kept in mind that the available literature scratches only the surface of what actually happens in AAS users. They underestimate the real, wanted and untoward effects of AAS administration. In most well designed investigations, the duration and dosages of AAS administration are far below daily practices in gyms or on the field. As a result, the observations underestimate the true effects since it has been established that dose-response relationships exist. On the other hand, case reports have the disadvantage of highlighting the most severe adverse effects and complications of AAS misuse, which may be primarily due to a temporal association rather than to a causal relationship. In the observational (cross-sectional as well as longitudinal) studies, selection bias may be an important confounder because of the lack of random assignment of participants to the AAS use or non-use group. Furthermore, since most drugs are obtained from the black market, quality is not guaranteed and polydrug use excludes the possibility of attributing the observed effects to a single drug. However, with respect to the methodological considerations raised, a review of the available literature on wanted and adverse effects AAS in athletes is provided.

3. Effects of AAS in Athletes

Soon after the development of synthetic AAS, these drugs were discovered by athletes for their muscle building and performance enhancing properties. Since the 1960s many researchers have investigated the effects of these drugs in athletes. However, many laboratory studies have the disadvantage of not mimicking actual AAS abuse habits among athletes, especially since the dosages self-administered increased dramatically in the last few decades. For example, most of the early, well designed studies assessed one drug in a therapeutic dose, while athletes are now used to self-administering polydrug regimens in dosages that may be 5–20 times higher than in most studies.[6,13,35] However, designing high standard scientific studies that approximate actual AAS abuse habits is precluded by ethical considerations. This emphasises the need for research designs that mimic real sport habits. In recent decades, this problem was addressed by studying the self-administration regimens of athletes. Nevertheless, the actual doses and regimens taken currently are much higher than described in those studies. Therefore, when reviewing the scientific literature, one has to

take into account that the current scientific knowledge of the effects of AAS may provide only a glimpse of the actual effects of these doping agents in athletes.

3.1 Body Composition

3.1.1 Introduction

For many years the effects of AAS on body composition in athletes has been of interest to many scientists. In most studies, body composition was determined using the two-compartment model, dividing the body into lean and fat mass. The method most frequently applied was measurement of four skinfolds from which the percentage of fat was estimated.[36-69] In a minority of AAS studies underwater weighing, previously recognised as the gold standard, was used for the determination of body composition.[44,50,70,71] More recently, three-compartment[51,52] as well as four-compartment methods, the contemporary gold standard, have been applied.[72,73]

3.1.2 Bodyweight

Although many strength athletes frequently report increments of about 10–15kg of bodyweight due to AAS administration, such alterations have not been documented in well designed prospective studies. Most studies show that bodyweight may increase by 2–5kg as a result of short-term (<10 weeks) AAS use.[53-56,59,63,69] The most pronounced average gain of bodyweight was reported by Casner and coworkers[70] after 6 weeks of stanozolol administration (table I). However, in a case report, an increase of 12.7kg over a 2-year AAS administration period was registered.[74]

3.1.3 Body Dimensions

Body dimensions may be affected by AAS administration. Although in some studies no alterations of circumferences could be observed,[37,44,45,50,60,65,68] most research showed that AAS induced alterations of body dimensions (table II).[49,51-56,59,67,69,77,78] The largest gains of circumferences can be found at the neck, thorax, shoulders and upper arm and may in part depend on the drugs and doses used.[49,51-56,59,67,69,77,78]

3.1.4 Lean Body Mass

Apart from a single exception,[36] no study was able to elucidate significant fat mass decrements.[36,51-54,59,71,75-77,79] Therefore, the alteration of bodyweight may be attributed mainly to an increase of lean mass. In this light, Kouri and coworkers[80] reported interesting preliminary data, indicating that AAS users may be distinguished from non-users by calculation of the fat-free mass index, a formula incorporating fat-free mass and height. The effects on lean body mass have been shown to be dose dependent[51,52,79] and regional differences in expression of the AAS-induced gain in lean body mass have been demonstrated.[51,52,81,82]

For many years the precise composition of the increased lean mass was not established. Although AAS have been demonstrated to stimulate protein synthesis,[83] the effects on muscle tissue could not be established. It has only been in the last decade that clear evidence for the muscle building properties of AAS in normal males and athletes became available.[72,73,77,79,84-89]

It has also been proposed that an increase of blood volume[90] and/or water retention[53,54] due to AAS use may occur in normal men, although recent research could not confirm such findings.[72,73]

3.1.5 Fat Mass

Since AAS were found to reduce fat mass in animal studies, athletes concluded that this might also occur in humans. However, research could not support this claim, but revealed the opposite[37,43,44,49-52,59,69,76] (table III). In three studies, a reduction in the percentage of fat could be observed; however, this was not reflected in a decrease of fat mass.[36,52,71] Therefore, the change in percentage fat can be attributed to the increase of lean body mass (table III). Conversely, personal observations revealed that strength athletes combine low caloric intake with concurrent AAS intake. The rationale for such regimens is that the athletes aim to reduce fat mass with simultaneous maintenance of muscle mass.

3.1.6 Muscle

The most prevalent reason for athletes initiating AAS use is to promote muscle mass and strength. A

Table I. Studies on the effects of strength training with androgenic-anabolic steroids (AAS) on bodyweight

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Bodyweight (kg)
Studies that found an increase of bodyweight					
Steinbach[66] (1968)	Blinding unclear, co	125 young adults	Metandienone (methandrostenolone) [3× per wk; 3mg each administration]	3mo	Metandienone: +1.24 Controls: +0.73 Metandienone + training: +1.67 Placebo + training: +0.73 Placebo: +0.63
Johnson & O'Shea[56] (1969)	nb, co	24 men inexperienced in strength training	Metandienone (10 mg/day PO)	3 wks	+2.48
O'Shea & Winkler[63] (1970)	nb, nc	3 weightlifters	Oxandrolone (10 mg/day PO)	6 wks	+4.8 (no statistics)
Casner et al.[70] (1971)	db, pc	27 young men	Stanozolol (6 mg/day PO)	2 × 3 wks (interspersed by 1wk no drug)	+7.0
O'Shea[62] (1971)	db, pc	18 experienced (>1y) weightlifters	Metandienone (10 mg/day PO)	4 wks	+3.9
Bowers & Reardon[42] (1972)	sb, c	18 strength athletes	Metandienone (10 mg/day PO)	3 wks	Significant (data not reported)
Johnson et al.[55] (1972)	db, c	31 students	Metandienone (10 g/day PO)	3 wks	+2.366
O'Shea[61] (1974)	sb, c	18 weightlifters (1–2y experience)	Stanozolol (8 mg/day PO)	5 wks	+2.8
Stamford & Moffat[65] (1974)	sb, pc	24 experienced (>2 junior) weight trainers	Metandienone (20 mg/day PO)	4 wks	+2.26
Freed et al.[47] (1975)	db, co, pc	13 weightlifters	Metandienone (10 or 25 mg/day PO)	6 wks	Significant (data not reported)
Win-May & Mya-Tu[69] (1975)	db, pc	31 students	Metandienone (5 mg/day PO)	13 wks	+2.4
Hervey et al.[53] (1976)	db, co, pc	11 physical education students	Metandienone (100 mg/day PO)	6 wks	+3.3
Hervey et al.[54] (1981)	db, co, pc	7 experienced weightlifters	Metandienone (100 mg/day PO)	6 wks	+2.32
Alén et al.[75] (1984)	nb, co	11 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	24 wks	+5.1
Alén & Häkkinen[36] (1987)	nb, co	9 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	6mo	+4.9

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Table I. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Bodyweight (kg)
Friedl et al.[49] (1991)	r, db, pc	30 physically active soldiers (9 resistance exercise, 1 cyclist, 20 running)	Testosterone enantate (100 mg/wk IM) [n = 8] Testosterone enantate (300 mg/wk IM) [n = 7] ND (100 mg/wk IM) [n = 8] ND (300 mg/wk IM) [n = 7]	6 wks	T-100: NS T-300: +3.4 ND-100: +2.7 ND-300: +3.3
Kuipers et al.[59] (1991)	nb	7 experienced bodybuilders	Polydrug use: several AAS (mean ± 200 mg/wk PO and IM) or testosterone (mean ± 2000 mg/wk IM)	10 wks	+3.9
Kuipers et al.[59] (1991)	r, db, pc	14 experienced bodybuilders	ND (start with 1 × 200mg IM; thereafter, 100 mg/wk IM for 7 wks)	8 wks	+3.7
Kuipers et al.[59] (1991)	r, db, co, pc	5 experienced bodybuilders	ND (start with 1 × 200mg IM; thereafter, 100 mg/wk IM for 7 wks)	8 wks	+3.5
Forbes et al.[76] (1992)	nb	7 untrained males	Testosterone enantate (mean cumulative dose was 42 mg/kg per subject; range 39–49 mg/kg)	12 wks	+4.1
Bhasin et al.[77] (1996)	r, db, pc	40 untrained adult males	Testosterone enantate (600 mg/wk IM)	10 wks	T + training: +6.0kg T: +3.5kg
Giorgi et al.[78] (1999)	r, db, pc	21 weight-trained subjects	Testosterone enantate (3.5 mg/kg bodyweight IM)	12 wks	+4.2
Hartgens et al.[51] (2001)	r, db, pc	16 bodybuilders	ND (200 mg/wk IM)	8 wks	+2.6
Hartgens et al.[52] (2001)	nb	35 strength athletes	Polydrug regimens (several AAS and/or T simultaneously, PO and/or IM)	8 wks and 12–16 wks	8 wks: +4.4 12–16 wks: +4.5
Studies that found no effect on bodyweight					
Fowler et al.[45] (1965)	db, pc	47 men (10 rugby players, 37 untrained students)	Methyl androstenolone acetate (20 mg/day PO)	16 wks	NS
Weiss & Müller[68] (1968)	NA	32 students	Metandienone (10 mg/day PO)	17 days	NS
Fahey & Brown[44] (1973)	db, pc	28 students	ND (1 mg/kg per 3 wks IM; injections in wks 2, 5 and 7)	9 wks study period	NS
Ward[71] (1973)	sb, pc	16 students experienced in strength training	Metandienone (10 mg/day PO)	4 wks	NS
Golding et al.[50] (1974)	db, c	40 experienced weightlifters	Metandienone (10 mg/day PO)	3 × 4 wks (3 wks AAS, 1wk no AAS)	NS
Strømme et al.[67] (1974)	db, pc	21 students	Mesterolone (75 mg/day) [first 4 wks: 75 mg/day PO; last 4 wks: 150 mg/day PO]	8 wks	NS
Loughton & Ruhling[60] (1977)	db, pc, s	6 untrained males and 6 wrestlers	Metandienone (10 mg/day PO for the first 3 wks; 5 mg/day for the last 3 wks)	6 wks	NS
Crist et al.[43] (1983)	db, co, pc	9 experienced strength athletes	Testosterone cipionate (100 mg/wk IM) ND (100 mg/wk IM) Placebo	Each drug for 3 wks	NS

c = controlled; **co** = crossover; **db** = double-blind; **IM** = intramuscular; **NA** = not available; **nb** = non-blind; **nc** = not controlled; **ND** = nandrolone decanoate; **NS** = not significant; **pc** = placebo-controlled; **PO** = oral; **r** = randomised; **s** = stratification; **sb** = single-blind; **T** = testosterone.

Table II. Studies on the effects of strength training with androgenic-anabolic steroids (AAS) on circumferences

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Circumferences (cm)
Studies that found an increase of circumferences					
Johnson & O'Shea[56] (1969)	nb, co	24 men inexperienced in strength training	Metandienone (methandrostenolone) [10 mg/day PO]	3 wks	Biceps: +1.35 Calf: +2.36 Forearm: NS Waist: NS Upper thigh: NS
Bowers & Reardon[42] (1972)	sb, c	18 strength athletes	Metandienone (10 mg/day PO)	3 wks	Biceps and forearm: NS
Johnson et al.[55] (1972)	db, c	31 students	Metandienone (10 g/day PO)	3 wks	Left calf: +0.491 Right calf, thigh, upper arm and lower arm: NS (compared with placebo)
Strømme et al.[67] (1974)	db, pc	21 students	Mesterolone (75 mg/day) [first 4 wks: 75 mg/day PO; last 4 wks: 150 mg/day PO]	8 wks	Thigh: +1.4 Arm: NS
Win-May & Mya-Tu[69] (1975)	db, pc	31 students	Metandienone (5 mg/day PO)	13 wks	Arm relaxed: +1.2 Arm contracted: +1.1 Thigh: +1.5 Calf: +0.9 Chest (inspiration): +1.3 Chest (expiration): +1.0
Hervey et al.[53] (1976)	db, co, pc	11 physical education students	Metandienone (100 mg/day PO)	6 wks	Arm: +1.33 Thigh: +1.34 Calf: +0.80
Hervey et al.[54] (1981)	db, co, pc	7 experienced weightlifters	Metandienone (100 mg/day PO)	6 wks	Arm: +1.07 Thigh: +1.11 Calf: NS

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Table II. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Circumferences (cm)
Friedl et al.[49] (1991)	r, db, pc	30 physically active soldiers (9 resistance exercise, 1 cyclist, 20 running)	Testosterone enantate (100 mg/wk IM) [n = 8] Testosterone enantate (300 mg/wk IM) [n = 7] ND (100 mg/wk IM) [n = 8] ND (300 mg/wk IM) [n = 7]	6 wks	15 CF measured: T-300: shoulder +3.3 ND-300: shoulder +3.8 ND-300: thorax (expiration) +3.9 All other CF: NS
Kuipers et al.[59] (1991)	nb	7 experienced bodybuilders	Polydrug use: several AAS (mean ± 200 mg/wk PO and IM) or testosterone (mean ± 2000 mg/wk IM)	10 wks	Neck: +1.0 Thorax: +2.5 Upper arm: +1.2 Forearm: +1.2 Thigh: +1.6 5 CF unchanged
Kuipers et al.[59] (1991)	r, db, pc	14 experienced bodybuilders	ND (start with 1 × 200mg IM; thereafter, 100 mg/wk IM for 7 wks)	8 wks	Neck: +0.9 Thorax: +4.1 Waist: +1.6 Forearm: +0.7 Thigh: +1.3 6 CF unchanged
Kuipers et al.[59] (1991)	r, db, co, pc	5 experienced bodybuilders	ND (start with 1 × 200mg IM; thereafter, 100 mg/wk IM for 7 wks)	8 wks	Neck: +0.7 Upper arm: +1.1 9 CF unchanged
Bhasin et al.[77] (1996)	r, db, pc	40 untrained men	Testosterone enantate (600 mg/wk IM)	10 wks	NA (increased without specification)
Giorgi et al.[78] (1999)	r, db, pc	21 weight-trained athletes	Testosterone enantate (3.5 mg/kg bodyweight IM)	12 wks	Thigh: NS Chest: NS Arm: +1.1 Calf: NS Abdomen: NS
Hartgens et al.[51] (2001)	r, db, pc	16 bodybuilders	ND (200 mg/wk IM)	8 wks	Neck: +0.9 Thorax, abdomen, buttocks, arm, forearm, thigh, calf: NS

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Table II. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Circumferences (cm)
Hartgens et al.[52] (2001)	nb	35 strength athletes	Polydrug regimens (several AAS and/or T simultaneously, PO and/or IM)	8 wks	Neck: +1.3 Upper arm (relaxed): +1.9 Upper arm (contracted): +1.5 Forearm: +1.1 Wrist: +0.3 Thigh(1): +2.2 Thigh(2): +2.2 Lower leg: +0.9 Thorax, waist, buttocks: NS
				12–16 wks	Comparable data to 8 wks
Studies that found no effect on circumferences					
Fowler et al.[45] (1965)	db, pc	47 men (10 rugby players, 37 untrained students)	Methyl androstenolone acetate (20 mg/day PO)	16 wks	Limb circumferences (measured limbs unknown): NS
Weiss & Müller[68] (1968)	NA	32 students	Metandienone (10 mg/day PO)	17 days	Upper arm relaxed and contracted: NS
Fahey & Brown[44] (1973)	db, pc	28 students	ND (1 mg/kg per 3 wks IM; injections in wks 2, 5 and 7)	9 wks study period	Arms, waist, chest, thighs: all NS
Golding et al.[50] (1974)	db, c	40 experienced weightlifters	Metandienone (10 mg/day PO)	3 × 4 wks (3 wks AAS, 1wk no AAS)	10 CF of thorax and limbs: all NS
Stamford & Moffat[65] (1974)	sb, pc	24 experienced (>2 junior) weight trainers	Metandienone (20 mg/day PO)	4 wks	Upper arm: NS Thigh: NS
Loughton & Ruhling[60] (1977)	db, pc, s	6 untrained males and 6 wrestlers	Metandienone (first 3 wks: 10 mg/day PO; last 3 wks: 5 mg/day)	6 wks	Calf, thigh, forearm, chest, arm: all NS
Alén et al.[37] (1984)	nb, co	11 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	24 wks	Thigh: NS Arms: NS

c = controlled; **CF** = circumference; **co** = crossover; **db** = double-blind; **IM** = intramuscular; **NA** = not available; **nb** = non-blind; **ND** = nandrolone decanoate; **NS** = not significant; **pc** = placebo-controlled; **PO** = oral; **r** = randomised; **s** = stratification; **sb** = single-blind; **T** = testosterone.

Table III. Studies on the effects of strength training with androgenic-anabolic steroids (AAS) on lean body mass (LBM)

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	LBM (kg)	LBM method
Studies that found an increase of LBM						
Ward[71] (1973)	sb, pc	16 students experienced in strength training	Metandienone (methandrostenolone) [10 mg/day PO]	4 wks	+3.1	HD
Hervey et al.[53] (1976)	db, co, pc	11 physical education students	Metandienone (100 mg/day PO)	6 wks	Dependent on method: +2.4 (HD) +6.3 (total body potassium) +3.5 (skinfolds)	Three methods: HD total body potassium skinfolds
Hervey et al.[54] (1981)	db, co, pc	7 experienced weightlifters	Metandienone (100 mg/day PO)	6 wks	+3.13	HD
Alén et al.[37] (1984)	nb, co	11 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	24 wks	+7.8	Skinfolds
Alén & Häkkinen[36] (1987)	nb, co	9 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	6mo	+8.7	Skinfolds
Kuipers et al.[59] (1991)	nb	7 experienced bodybuilders	Polydrug use: several AAS (mean ± 200 mg/wk PO and IM) or testosterone (mean ± 2000 mg/wk IM)	10 wks	+3.6	Skinfolds
Kuipers et al.[59] (1991)	r, db, pc	14 experienced bodybuilders	ND (start with 1 × 200mg IM; thereafter, 100 mg/wk IM for 7 wks)	8 wks	+2.7	Skinfolds
Kuipers et al.[59] (1991)	r, db, co, pc	5 experienced bodybuilders	ND (start with 1 × 200mg IM; thereafter, 100 mg/wk IM for 7 wks)	8 wks	+2.7	Skinfolds
Forbes et al.[76] (1992)	nb	7 untrained males	Testosterone enantate (mean cumulative dose was 42 mg/kg per subject; range 39–49 mg/kg)	12 wks	+7.5	Potassium 40 counting
Bhasin et al.[77] (1996)	r, db, pc	40 untrained adult males	Testosterone enantate (600 mg/wk IM)	10 wks	T + training: +6.1 T: +3.2	HD
Hartgens et al.[51] (2001)	r, db, pc	16 bodybuilders	ND (200 mg/wk IM)	8 wks	+3.6	Skinfolds
Hartgens et al.[52] (2001)	nb	35 strength athletes	Polydrug regimens (several AAS and/or T simultaneously, PO and/or IM	8 wks 12–16 wks	8 wks: +4.5 12–16 wks: +4.5	Skinfolds

Continued next page

Table III. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	LBM (kg)	LBM method
Studies that found no effect on LBM						
Casner et al.[70] (1971)	db, pc	27 young men	Stanozolol (6 mg/day PO)	2 × 3 wks (interspersed by 1wk no drug)	NS	HD
Fahey & Brown[44] (1973)	db, pc	28 students	ND (1 mg/kg per 3 wks IM; injections in wk 2, 5 and 7)	9 wks study period	NS	HD
Golding et al.[50] (1974)	db, pc	40 experienced weightlifters	Metandienone (10 mg/day PO)	3 × 4 wks (3 wks AAS, 1wk no AAS)	NS	HD
Crist et al.[43] (1983)	db, co, pc	9 experienced strength athletes	Testosterone cipionate (100 mg/wk IM) ND (100 mg/wk IM) Placebo	Each drug for 3 wks	NS	HD

co = crossover; **db** = double-blind; **HD** = hydrodensitometry; **IM** = intramuscular; **nb** = non-blind; **ND** = nandrolone decanoate; **NS** = not significant; **pc** = placebo controlled; **PO** = oral; **r** = randomised; **sb** = single-blind; **T** = testosterone.

recent series of well designed studies by Bhasin and coworkers[77] investigated the effects of exogenous testosterone administration, with and without an accompanying strength training programme, on muscle tissue in eugonadal males. Through use of magnetic resonance imaging measurements they observed that 10 weeks of testosterone administration (600 mg/week) may lead to increments of the area of the triceps brachii and quadriceps muscles. The gains in muscle mass were larger when testosterone administration was combined with a strength training programme, and may lead to increments of approximately 15% of the area of the triceps brachii and quadriceps muscles.[77] In another study, different dosages of testosterone enantate (25, 50, 125, 300 and 600 mg/week) for 10 weeks were administered to non-exercising volunteers. It was found that the effects on thigh muscle volume and quadriceps muscle volume were highly dose dependent.[79] Giorgi et al.[78] registered gains in muscle mass of rectus femoris muscle and the triceps brachii muscle by means of ultrasonography.[78] Van Marken Lichtenbelt and coworkers[73] demonstrated that the effects of AAS on lean body mass could be attributed to real muscle growth, since no alterations of hydrational status of lean body mass could be observed.

Because of the relationship between strength and fast twitch muscle fibres it has been supposed that AAS would affect type II (fast twitch) muscle fibres more than type I (slow twitch) fibres. In two cross-sectional studies investigating muscular adaptation at the cellular level in strength athletes, the largest difference in muscle fibre size between AAS users and non-users was observed in type I muscle fibres of the vastus lateralis[91] and the trapezius muscle[86] as a result of long-term AAS self-administration. On the other hand, prospective studies presented equivocal results. In athletes self-administering high doses of several AAS simultaneously, studies found increments of type I muscle fibres of the vastus lateralis muscle, whereas the type II fibres remained unaltered.[37,59,88] Hartgens et al.[85] demonstrated that polydrug regimens for 8 weeks increased muscle fibre size of the deltoid muscle in strength ath-

letes, with the most profound effect on the type II fibres reflected by a growth of nearly 15%. Administration of a single anabolic steroid (i.e. intramuscular nandrolone decanoate 200 mg/week) for 8 weeks, however, had no effect on the size of deltoid muscle fibres.[85] In muscle biopsy samples from the vastus lateralis, Sinha-Hikim et al.[89] found that administration of testosterone 300 and 600mg increased the cross-sectional areas of type I muscle fibres and the myonuclear number per fibre, while type II muscle fibres were only enlarged after the 600mg administration regimen in eugonadal males.[89] Lower doses of testosterone 25, 50 and 125 mg/week had no effects on muscle fibre cross-sectional areas.[89]

From these studies it can be concluded that AAS administration may increase muscle mass in a dose-dependent relationship, but independent of the regimen used (single drug vs polydrug regimen). Whether type I or type II muscle fibres are more profoundly affected is not clear yet, but that might be related to the substance(s) and/or dose administered. The underlying mechanism has been the subject of study by Kadi and coworkers.[81,82,86,87] Their research showed that the increase in muscle mass can be attributed to muscle hypertrophy and also the formation of new muscle fibres.[81,87] They also hypothesised that the fundamental process for muscle fibre growth seemed to be the incorporation of the satellite cells into pre-existing fibres to maintain a constant nucleus to cytoplasm ratio. Moreover, key roles seem to be played by satellite cells (i.e. they are enhanced by AAS administration) and androgen receptors. Androgen receptors are expressed in myonuclei of muscle fibres and in capillaries and are more present in neck and shoulder muscles than in limb muscles. AAS administration induces an increase in androgen receptor-containing myonuclei in the shoulder girdle muscles but not in the vastus lateralis,[81,82] although Sinha-Hikim et al.[89] demonstrated that high doses of testosterone were also able to increase the myonuclear number per fibre in the vastus lateralis muscle. Recently, Sinha-Hikim and associates[92] observed that muscle hypertrophy induced by exogenous testosterone administration was associated with an increase in satellite cell number, changes in satellite cell ultrastructure and a proportionate increase in myonuclear number. These observations may, at least partially, explain the regional differences in body changes and muscle fibre adaptation.[82,85]

3.1.7 Body Composition Changes After Drug Withdrawal

After drug withdrawal the alterations of body composition fade away slowly, but may be partially present for time periods up to 3 months.[37,51,52,59,76] However, on the basis of scientific data, the final net result of short-term AAS administration on body composition seems to be rather small. From our own observations, this seems to be particularly true for recreational athletes as they are not capable of maintaining the nutritional intake and training workload of the level required for significant body composition changes.[91] On the other hand, short-term AAS self-administration in these athletes results in fast gains and is, therefore, very attractive to them.

3.1.8 Summary

In strength athletes, both short- and long-term AAS administration will increase lean body mass significantly, which may contribute to an increase of muscle mass. In the upper body, type II muscle fibres seem to increase more than type I fibres after short-term AAS use, whereas in the thigh the opposite may occur. Conversely, type I fibres may grow after persistent long-term AAS abuse. The hydration of the lean mass remains unaffected, although small increments of blood volume cannot be ruled out. Also, fat mass does is not altered by AAS use. The effects on lean body mass are dose dependent, although it is not clear which drug administration regimen leads to the most pronounced results. The administration of therapeutic doses of a single steroid for periods up to 10 weeks does not seem to exert measurable effects on muscle mass, although body changes are observable. The upper region of the body (thorax, neck, shoulders and upper arm) seems to be more susceptible for AAS than other body regions because of predominance of androgen receptors in the upper body. After drug withdrawal

the effects fade away slowly, but may persist for more than 6–12 weeks after cessation of AAS use.

3.2 Strength

Strength is an important quality for many sports. Strength is relevant not only in specifically strength sports (e.g. weightlifting), but also in many others such as rowing, sprinting and cycling. Many researchers have investigated the effects of AAS on strength[36-40,42-45,48-50,54-56,58,60-71,77,78] (table IV). Several of these studies do not meet the quality standards for scientific research. Based on available well designed studies it can be concluded that AAS enhance the effects of strength training. The observed improvements were in the range of 5–20% of baseline strength, largely depending on the drugs and dose used as well as the administration period. Although most research has focused on absolute strength determined by one repetition maximum or isokinetic strength, one study tested the effects on canoeing capacities. Rademacher et al.[93] reported that in male canoeists, 6 weeks of Oral-Turinabol [1] administration improved strength and performance measured by canoe ergometry with 6% and 9%, respectively.[93]

For many years it was assumed that AAS only exerted significant effects in experienced strength athletes, particularly based on the studies of Hervey and coworkers.[53,54] However, recently, Bhasin et al.[77] demonstrated that even in novice athletes a 10-week strength training programme accompanied by testosterone administration may improve strength more than strength training alone does. Previously, a literature review by Elashof et al.[94] concluded that strength improvements in experienced strength athletes may be only slightly larger than in novice athletes. Moreover, injectable testosterone (600 mg/week intramuscularly) has clearly been demonstrated to improve strength even without a concomitant exercise training programme.[77]

From the available literature it seems impossible to predict which drugs and dose will exert the best improvements in strength. For example, metandienone (methandrostenolone) is the most frequently investigated drug and studies differed with respect to dose and duration of drug administration.[38-40,42,48,50,54-56,60,62,65,66,68,69,71] The majority of studies observed significant strength gains, especially for bench press performance, during metandienone administration,[38-40,42,48,54-56,62,65,66,69,71] whereas in four studies no strength alterations were reported.[50,53,60,68] The strength gains did not seem to depend on duration of metandienone use since changes could already be observed after 3 weeks' administration of 10 mg/day.[42,55,56] The impact of the administered dose is difficult to assess because in most research a dose of 10 mg/day was investigated with some reporting strength gains,[38,42,48,55,56,62,66,71] while others could not find such improvements.[50,60,68] Nevertheless, it seems likely that dosages exceeding 10 mg/day will increase strength,[39,48,54,65] although the results from one study not reporting strength improvements are difficult to explain.[53]

Few studies investigated the effects of injectable steroids. Testosterone enantate has been demonstrated to consistently enhance strength after administration of daily dosages of 300mg and over[49,79] or by using 3.5 mg/kg bodyweight.[78] Friedl et al.[49] also demonstrated that androgenic substances influence strength more than anabolic agents. With respect to strength enhancement it remains debatable whether polydrug regimens are superior to single drug administration,[36,37,49,77] although the former increase muscle dimensions, which are closely related to strength, more than the latter.[85] However, we should emphasise again that laboratory studies may not adequately mimic the actual AAS-induced improvements of strength since the drugs and doses investigated in most studies are not in agreement with current steroid administration regimens by AAS abusers.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table IV. Studies on the effects of strength training with androgenic-anabolic steroids (AAS) on strength

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Strength (kg)	Method strength measurement
Studies that found an increase of strength						
Steinbach[66] (1968)	Blinding unclear, co	125 young adults	Metandienone (methandrostenolone) [3× per wk; 3mg each administration]	3mo	Isometric strength elbow flexion: + Hip flexors: +	Strain gauge
Johnson & O'Shea[56] (1969)	nb, co	24 men inexperienced in strength training	Metandienone (10 mg/day PO)	3 wks	BP: +12	1RM
					SQ: +23	1RM
					Shoulder flexion: +21.1	Cabletensiometer
					Elbow flexion: +16.2	Cabletensiometer
					Elbow extension: NS	Cabletensiometer
					Knee flexion: NS	Cabletensiometer
					Knee extension: NS	Cabletensiometer
O'Shea & Winkler[63] (1970)	nb, nc	3 weightlifters	Oxandrolone (10 mg/day PO)	6 wks	BP and SQ Standing press Incline press Power clean Two-hand snatch Clean and jerk All improved (no statistics)	1RM
O'Shea[62] (1971)	db, pc	18 experienced (>1y) weightlifters	Metandienone (10 mg/day PO)	4 wks	BP: +16.9 SQ: +18.2	1RM
Bowers & Reardon[42] (1972)	sb, c	18 strength athletes	Metandienone (10 mg/day PO)	3 wks	BP, SQ	1RM
Johnson et al.[55] (1972)	db, c	31 students	Metandienone (10 g/day PO)	3 wks	BP: +	1RM

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Table IV. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Strength (kg)	Method strength measurement
					SQ: +	Cabletensiometer
					Knee extension: +	
					Shoulder flexion: +	
					Elbow flexion: +	
Ariel[38] (1973)	db, pc	6 experienced (>2 junior) strength athletes	Metandienone (10 mg/day PO)	4 wks	BP: +	1RM
					SQ: +	
					SP: +	
					MP: +	
					Total: +	
Fahey & Brown[44] (1973)	db, pc	28 students	ND (1 mg/kg per 3 wks IM; injections in wk 2, 5 and 7)	9 wks study period	Elbow extension: +	Isokinetic
					Elbow flexion: +	Isokinetic
					Shoulder extension: +	Isokinetic
					Shoulder flexion: +	Isokinetic
					Knee extension: +	Isokinetic
					Knee flexion: +	Isokinetic
					Bench press: +	1RM
					Dead lift: +	1RM
Ward[71] (1973)	sb, pc	16 students experienced in strength training	Metandienone (10 mg/day PO)	4 wks	BP: +15.6	1RM
					SQ: +23.6	
Ariel[40] (1974)	db, co, pc	10 students experienced in strength training	Metandienone (15 mg/day PO)	4 wks	BP: +	1RM
					SQ: +	
					CU: +	
					MP: +	

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Table IV. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Strength (kg)	Method strength measurement
O'Shea[61] (1974)	db, c	18 weightlifters (1–2y experience)	Stanozolol (8 mg/day PO)	5 wks	BP: +11.4 SQ: +21.6	1RM
Stamford & Moffat[65] (1974)	sb, pc	24 experienced (>2 junior) weight trainers	Metandienone (20 mg/day PO)	4 wks	BP: +7.17 kg 80% repetitions: NS SSI: NS	1RM Dynamometer
Freed et al.[48] (1975)	db, co, pc	13 weightlifters	Metandienone (10 or 25 mg/day PO)	6 wks	Several exercised	1RM (self-report by athletes' pre-study performance)
Win-May & Mya-Tu[69] (1975)	db, pc	31 students	Metandienone (5 mg/day PO)	13 wks	Sit-ups: + Pull-ups: + Standing broad-jump: + Handgrip dynamometer: +	NA
Keul et al.[58] (1976)	nb, nc	15 weightlifters	ND (50mg per 12 days IM)	2mo	Sum of improvements of BP, SQ and DL: +	1RM
Hervey et al.[54] (1981)	db, co, pc	7 experienced weightlifters	Metandienone (100 mg/day PO)	6 wks	Leg training: +14.2 Arm training: +13.4 Grip strength: NS Leg strength: NS Arm strength: NS	Dynamometer, 1RM
Alén et al.[37] (1984)	nb, co	11 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	24 wks	SQ: +35 Maximal bilateral isometric strength: +632.8N	1RM electromechanical dynamometer

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Table IV. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Strength (kg)	Method strength measurement
Alén & Häkkinen[36] (1987)	nb, co	9 experienced strength athletes	Polydrug use: several AAS (mean ± 220 mg/wk PO) and testosterone (mean ± 180 mg/wk IM)	6mo	Maximal bilateral isometric strength: +836N	Electromechanical dynamometer
Friedl et al.[49] (1991)	r, db, pc	30 physically active soldiers (9 resistance exercise, 1 cyclist, 20 running)	Testosterone enantate (100 mg/wk IM) [n = 8] Testosterone enantate (300 mg/wk IM) [n = 7] ND (100 mg/wk IM) [n = 8] ND (300 mg/wk IM) [n = 7]	6 wks	T-300: elbow 240/sec +17.3% T-300: knee 60/sec +11.6% All other measurements with T-100, ND-100 and ND-300: NS	Isokinetic: elbow flexion 60/s elbow flexion 240/s knee extension 60/s knee extension 240/s
Bhasin et al.[77] (1996)	r, db, pc	40 untrained men	Testosterone enantate (600 mg/wk IM)	10 wks	BP, T + training: +22 BP, placebo + training: +10 BP, T: NS BP, placebo: NS SQ, T + training: +38 SQ, placebo + training: +25 SQ, T: + 8 SQ, placebo: NS	1RM
Giorgi et al.[78] (1999)	r, db, pc	21 weight-trained subjects	Testosterone enantate (3.5 mg/kg bodyweight IM)	12 wks	BP: +21	1RM

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Table IV. Contd

Study (year)	Study design	Subjects	AAS used (dose)	Duration of AAS use	Strength (kg)	Method strength measurement
Studies that found no effect on strength						
Samuels et al.[64] (1942)	sb, co, pc	4 untrained men	Methyltestosterone (first 3 wks: 50 mg/day PO; 4th wk: 200 mg/day)	4 wks	Grip (in 3 of 4 subjects): NS	Dynamometer
Fowler et al.[45] (1965)	db, pc	47 men (10 rugby players, 37 untrained students)	Methyl androstenolone acetate (20 mg/day PO)	16 wks	Grip, pull-up, push-up: NS 13 muscle groups: NS	Cabletensiometer
Weiss and Müller[68] (1968)	NA	32 students	Metandienone (10 mg/day PO)	17 days	Arm extension: NS	Dynamometer
Casner et al.[70] (1971)	db, pc	27 young men	Stanozolol (6 mg/day PO)	2 × 3 wks (interspersed by 1wk no drug)	Hand grip strength: NS Leg strength: NS Trunk strength: NS Arm-forearm strength: NS	Hydraulic system
Golding et al.[50] (1974)	db, c	40 experienced weightlifters	Metandienone (10 mg/day PO)	3 × 4 wks (3 wks AAS, 1wk no AAS)	BP, CU, biceps, quadriceps, grip: all NS	1RM, static strength gauge
Strømme et al.[67] (1974)	db, pc	21 students	Mesterolone (75 mg/day) [first 4 wks: 75 mg/day PO; last 4 wks 150 mg/day PO]	8 wks	Knee extension: NS Trunk extension: NS Trunk flexion: NS Elbow flexion: NS Knee-hip extension: NS	Strain gauge meter
Loughton & Ruhling[60] (1977)	db, pc, s	6 untrained males and 6 wrestlers	Metandienone (first 3 wks: 10 mg/day PO; last 3 wks: 5 mg/day)	6 wks	BP, SQ, leg press arms, legs: all NS	Cabletensiometer, 1RM
Crist et al.[43] (1983)	db, co, pc	9 experienced strength athletes	Testosterone cipionate (100 mg/wk IM) ND (100 mg/wk IM) Placebo	Each drug for 3 wks	Elbow flexion/extension: NS Knee flexion/extension: NS Ankle flexion/extension: NS	Isokinetic

BP = bench press; **c** = controlled; **co** = crossover; **CU** = curl; **db** = double-blind; **DL** = dead lift; **IM** = intramuscular; **MP** = military press; **NA** = not available; **nb** = non-blind; **nc** = not controlled; **ND** = nandrolone decanoate; **NS** = not significant; **pc** = placebo-controlled; **PO** = oral; **r** = randomised; **RM** = repetition maximum; **sb** = single-blind; **SP** = sitting press; **SQ** = squat; **SSI** = static strength index; **T** = testosterone; **+** = significant increase.

3.3 Haematology and Endurance Performance

Soon after their introduction, AAS were registered for the treatment of several kinds of anaemia. Long-term treatment with AAS has been demonstrated to increase serum haemoglobin concentrations.[95] Because of the relationship between haemoglobin and endurance performance, athletes started to self-administer AAS. However, only two investigations were able to register AAS-induced alterations of haematology in athletes.[96,97] Alén[96] described increases in serum haemoglobin concentrations, haematocrit, mean corpuscular haemoglobin concentration and mean corpuscular haemoglobin, the number of white blood cells and platelets in athletes after 6 months' self-administration of high doses of AAS, whereas mean red cell volume remained unaltered.[96] More recently, Hartgens et al.[97] found an increase of platelet count after 8 weeks of AAS use, whereas all other haematological parameters remained unaffected.[97]

The majority of studies demonstrated that AAS were not able to increase endurance performance in athletes.[42,44,53,55,57,67,69,98] However, in two studies, an improvement of aerobic capacity was noticed.[56,58] Remarkably, the volunteers in both studies were strength athletes who did not train for endurance performance.[56,58]

The increase of anti-doping controls, the development of more advanced urinalysis techniques and the availability of recombinant human erythropoietin has led to the abandonment of the use of AAS for improvement of aerobic capacities among athletes.

3.4 Recovery

Many athletes report that AAS administration enhances recovery time from strenuous training. Unfortunately, the research done on this issue only studied indirect parameters that are associated with recovery time.[58,66,99-102] The investigation of Keul and coworkers[58] showed that exercise-induced increments of heart rate and serum lactate levels were significantly delayed with use of nandrolone decanoate. Additionally, after completion of the exercise session the return of the heart rate and lactate level to baseline values was faster in the AAS users.[58] On the other hand, administration of injectable testosterone enantate had no effect on serum levels of urea, ammonia, creatinine, creatine kinase (CK) and aspartate aminotransferase (ASAT), indicating that this substance did not affect regeneration in well trained endurance athletes.[98,103] Rozenek et al.[102] found higher androgen/cortisol ratios and lower plasma lactate levels in AAS users compared with non-users after completing a strength-training work out. The authors suggested that the lower subjective level of fatigue after training sessions could be attributed to AAS.[102] Boone et al.[99] concluded that AAS administration resulted in a diminished CK response and an altered stress response to a single bout of resistance exercise.[99] The CK response observed was in line with the previous findings of McKillop and coworkers.[100,101] Although in animals an enhanced recovery has been demonstrated after AAS administration,[104] research on the recovery rate in humans is too limited to draw definite conclusions yet.

4. Adverse Effects

It seems redundant to mention that abuse of AAS may affect health status. On the other hand, the many case reports in the literature indicate that a substantial number of athletes will not be deterred by the adverse effects and will accept the risks of (major) health damage. As mentioned previously, since most well designed studies are not able to address the AAS issue of real life, we want to emphasise that the untoward effects may be more pronounced than has been demonstrated in laboratory studies. Also, the extent of side effects in AAS users will be much larger than may be expected on the basis of the available scientific data.

Side effects can be divided in subjective and objective. First, we describe studies that focused on subjective perceived side effects. Later we discuss the undesired health effects that are open to objectification.

4.1 Self-Reported Adverse Effects

To date, only a few reports investigating the self-reported adverse effects in athletes using AAS have been published.[35,105-108] These reports employing questionnaires showed clearly that the majority of athletes experienced undesired health effects not only when on AAS, but also after drug withdrawal. These data are very valuable since they indicate the extent of self-reported untoward effects when using high doses of AAS in stacking regimens reflecting real-life AAS abuse. The side effects reported in at least 40% of the male subjects in these studies included increased sexual drive,[35,106,108] occurrence of acne,[108] increased body hair[108] and an increase in aggressive behaviour.[106] Furthermore, many other side effects affecting several body systems were mentioned by the steroid users. These include fluid retention, elevated blood pressure (BP), sleeplessness, increased irritability, decreased libido, increased appetite, enhanced transpiration, increased feeling of well-being, depressive mood states, loss of head hair and the occurrence of gynaecomastia.

Data relating to female athletes are very scanty.[35,105] Strauss et al.[105] interviewed ten females who all reported lowering of the voice brought on by AAS use. Furthermore, nine of ten females admitted increased growth of facial hair, enlargement of the clitoris and an increase in aggressiveness and appetite.[105] Recently, in the study by De Boer et al.,[35] nine of ten interviewed female athletes had experienced side effects due to steroid use.[35] The side effects reported were acne (50%), fluid retention (40%) and alteration of libido (50%). Other side effects were only mentioned by <20% of the women.[35] The discrepancy between the reported side effects in both studies can, at least in part, be attributed to the difference in substances and dosages used. The subjects in the study of Strauss et al.[105] self-administered more androgenic agents and used much higher doses than the female bodybuilders of DeBoer et al.'s[35] study which may be responsible for the masculinising effects. Of great concern is that athletes are not aware of many side effects during steroid administration, since several unwanted health effects may be detected only after thorough medical examination, including blood analysis.

4.2 The Reproductive System

Since AAS are derived from testosterone they exert important effects on the sex hormones and the reproductive system. They will suppress the hypothalamic-pituitary-gonadal axis, which acts as a feedback system. Consequently, exogenous administration of AAS will disturb the endogenous production of testosterone and gonadotrophins (luteinising hormone [LH] and follicle-stimulating hormone [FSH]). In males, suppression of gonadotropin production induces testicular atrophy and reduces semen production and quality. Studies have shown that the use of AAS may dramatically lower serum gonadotrophin concentrations;[36,77,79,109-111] a decline can be observed within 24 hours.[112] Serum testosterone levels will also decrease,[110,113] except when exogenous testosterone is administered in amounts usually practised by strength athletes.[109] However, Bhasin et al.[79] proved that a close dose-response relationship exists between the administered dose of testosterone and serum levels of testosterone.[79] Administration of weekly doses of intramuscular testosterone ≥300mg increase serum levels of testosterone and free testosterone, whereas weekly doses of 25 or 50mg resulted in lower serum levels of testosterone and free testosterone.[79] Previously, it has been demonstrated that the administration of high doses of testosterone in polydrug abusers will induce supraphysiological levels of serum total and free testosterone and estradiol.[109,114,115] Serum concentrations of androstenedione and dihydrotestosterone closely follow the same pattern.[116] The high serum levels of estradiol, androstenedione and dihydrotestosterone can be explained by peripheral conversion of AAS.[117]

The administration of supratherapeutic doses of AAS will reduce the quantity and quality of semen production in male athletes and may lead to infertility within months.[111,118,119] This is in agreement with the results of research into the use of androgens for contraceptive purposes in males, although this method of contraception is still experimental and not

yet reliable.[21] Once the steroid intake is stopped, the exact time needed for full recovery of reproductive function is not known and may vary depending on the doses taken and duration of AAS abuse. After long-term (6 months) polydrug administration, full recovery may take at least 4–5 months.[36,109,120] However, in some individuals complete restoration of normal reproductive function may take more than a year.[118] Long-term administration of high doses of AAS may provoke hypogonadotrophic hypogonadism, characterised by testicular atrophy, oligo- or azoospermia, low serum concentrations of LH and FSH, and of endogenous testosterone and precursors.[17,120] A number of athletes try to prevent or reverse this disturbance of the reproductive system by using human chorionic gonadotrophin or clomifene together with the AAS or immediately after the end of the AAS course, although scientific rationale for such regimens is not available. Treatment of hypogonadotrophic hypogonadism with human chorionic gonadotrophin resulted in a testicular responsiveness comparable with that in prepubertal boys.[120] On the other hand, in recent case studies it has been reported that clomifene may successfully restore AAS-induced pituitary-gonadal dysfunction[121] and treatment with both human chorionic gonadotrophin (hCG) and human menopausal gonadotrophins (hMG) reversed persistent azoospermia due to the misuse of AAS.[122] Moreover, Karila and coworkers[123] demonstrated that in AAS abusers spermatogenesis can be maintained by using hCG during an AAS course, although sperm quality may be impaired.

Another adverse effect is the occurrence of gynaecomastia in male athletes as a result of AAS abuse. Besides the pain that may accompany gynaecomastia, the cosmetic implications may be important for bodybuilders. Development of gynaecomastia is associated with the peripheral conversion of AAS to estrogens, as a result of the huge amounts of exogenous AAS administered.[13,124,125] In the early stages spontaneous regression may be expected, but in long-term cases surgical correction may be the only appropriate treatment.[13,126] A common practice among strength athletes is to accompany AAS abuse with self-administration of tamoxifen for the prevention of gynaecomastia. Nevertheless, scientific data do not support the effectiveness of this preventive method.[127]

Research exploring the effects of AAS in females is scarce; the administration of AAS will induce masculinisation in women. Female bodybuilders reported the development of acne vulgaris, changes in libido and alterations of the voice as the most pronounced adverse effects in the first weeks of AAS use.[35] Long-term AAS administration may induce loss of hair of the head, alterations of pubic hair growth and enlargement of the clitoris. Furthermore, menstrual irregularities and a reduction of the breasts usually occur. Finally, adolescents may be prone to early closure of growth plates resulting in premature stop of length growth.[13]

4.3 The Cardiovascular System

In recent years the abuse of AAS has been associated with the occurrence of serious cardiovascular events in healthy young athletes, including the development of cardiomyopathy, atrial fibrillation, QT dispersion, cerebrovascular accident, myocardial infarction, disturbances of the haemostatic system, ventricular thrombosis and systemic embolism, and acute heart failure.[128-136] Moreover, several reports associated AAS abuse with cardiac sudden death.[137-142] Although these reports must be interpreted with caution, they teach us to look thoroughly at the different mechanisms in which AAS abuse may affect the cardiovascular system. However, again, it should be remembered that in case reports the most dramatic side effects are often described and that they do not prove a causal relationship between AAS abuse and the disease condition or cardiac death.

Although these case reports may draw our attention to different ways in which the cardiovascular system may be affected by AAS, research has mainly focused on evaluation of risk factors for cardiovascular disease and examination of cardiac structure and function by echocardiography.

4.3.1 Blood Pressure

Several studies investigating different AAS regimens showed no alteration in BP in healthy strength athletes.[33,59,143-147] However, in other investigations, an elevation of systolic or diastolic BP has been observed as a result of the administration of high doses of AAS.[48,59,112,145,148-150] An elevation of BP may be present within 4 weeks of taking steroids.[149] The most pronounced increase of diastolic pressure was reported by Kuipers et al.[59] They found an increase from 74 to 86mm Hg due to 10 weeks of self-administration of high-dose AAS.[59] Increments of systolic BP of about 10[148] and 12mm Hg[59] in normotensive strength athletes due to AAS have been reported. After drug cessation the BP seems to return to pre-steroid levels within several weeks.[59] However, a recent prospective study by Hartgens et al.[144] could not confirm elevations of BP in athletes, even in those self-administering supratherapeutic doses of AAS for periods of up to 16 weeks.[144]

The available literature is not conclusive with respect to the effects of AAS on BP. It is suggested that elevations of systolic and/or diastolic BP may occur in some individuals; however, the effect does not seem to be consistent. Androgens seem to affect BP more than anabolic agents, although the exact mechanism remains to be established.[12,59,149] However, if elevations of BP occur they seem to be small and transient, indicating that the impact on health status of the athlete may be limited.

4.3.2 Lipoprotein Metabolism

Total Cholesterol

The effects of AAS on serum total cholesterol metabolism are not determined in detail yet. Most prospective studies, investigating either low or high doses of single drug use or polydrug administration for periods from 3 to 26 weeks, reported no alterations of serum total cholesterol levels.[48,59,63,151-157] Nevertheless, some studies found that AAS were able to induce an increase of serum total cholesterol levels,[158-160] whereas others observed a decrease.[161,162] The nature of this discrepancy of serum cholesterol response has yet to be established. However, the response of serum total cholesterol levels to nandrolone decanoate administration seems to be very consistent. The use of therapeutic and supratherapeutic doses of nandrolone decanoate does not seem to affect serum cholesterol levels.[59,143,163] In strength athletes, testosterone enantate administered by intramuscular injection may have no effect on serum total cholesterol levels after 3 weeks of administration,[164] but after 6 weeks a reduction of total cholesterol may occur.[165] On the other hand, supratherapeutic doses of another testosterone substance (i.e. testosterone cipionate) do not exert significant effects on serum total cholesterol levels.[166]

High-Density Lipoprotein-Cholesterol and its Subfractions

High-density lipoprotein (HDL)-cholesterol and its subfractions have been recognised as independent risk factors for the occurrence of cardiovascular disease.[167] There is strong evidence that AAS administration will induce remarkable reductions of the serum levels of these lipoproteins.[7,154,168-171] The suppressive effect varies between different androgenic-anabolic compounds, with decrements of HDL-cholesterol ranging from 39–70%.[168] The most pronounced suppression has been observed in serum levels of HDL2-cholesterol rather than HDL3-cholesterol,[145,154,165,172] with suppression ranging from 55–89% for HDL2-cholesterol and from 13–55% for HDL3-cholesterol.[154,168] The reduction of serum HDL-cholesterol levels is mediated by hepatic triglyceride lipase (HTGL), an enzyme that regulates serum lipids[173] and exposes the AAS-using athletes to an increased atherogenic risk.[7,154,173]

The orally taken 17-α-alkylated substances (such as stanozolol, oxymetholone and metandienone) exert much stronger effects than other AAS.[7,165] The decline of HDL-cholesterol can be observed within a few days of starting steroid administration.[165] After an initial strong negative effect, the suppression of the serum HDL-cholesterol and its subfractions continues at a more moderate level.[59,145,148,152,165] After 8 weeks of AAS administration no further decline of HDL-, HDL2- and HDL3-cholesterol can be observed.[154]

Short-term administration of androgens, such as testosterone enantate and cipionate, also depress serum HDL-cholesterol levels significantly.[165,166] Effects of testosterone supplementation on lipoproteins, however, have been shown to be dose dependent.[174] Singh et al.[174] demonstrated that intramuscular testosterone 600 mg/week reduced HDL-cholesterol levels, whereas lower doses did not exert any effect on lipoprotein profiles.[174] HDL-cholesterol suppression by 19-nortestosterone esters seem to follow another pattern since adverse effects in males have been demonstrated only after long-term administration, whereas in women alterations have been observed after short-term use of low doses. Parenteral administration of nandrolone decanoate for periods up to 2 months does not affect HDL-cholesterol and subfractions in healthy athletes.[59,154,163] However, in clinical studies this steroid was found to affect HDL-cholesterol metabolism unfavourably in male haemodialysis patients when administered for more than 6 months.[175] In women with postmenopausal osteoporosis a reduction of serum HDL-cholesterol levels was noticed even after 3 weeks.[176]

After steroid withdrawal, the disturbed lipid and lipoprotein profiles recover completely, although at least 4–12 weeks are needed for return to baseline values.[59,152,154,159,162] Hartgens and coworkers[154] demonstrated that recovery depends strongly on the duration of an AAS course.

Low-Density Lipoprotein-Cholesterol

In general, the administration of multiple AAS is likely to increase serum low-density lipoprotein (LDL)-cholesterol levels.[145,148,157,165,172] The elevation parallels the decrease of HDL-cholesterol and may be observed within a few days after initiation of steroid use.[165] Single anabolic steroid administration may exert different effects on serum LDL levels depending on the steroid and route of administration. Oral administration of stanozolol increased LDL levels,[165] whereas the intramuscular injections of testosterone cipionate or testosterone enantate did not alter LDL levels.[164,166]

Triglycerides

The effects on triglyceride metabolism appear to be more unequivocal. Most prospective studies in athletes did not observe any alteration of serum triglyceride levels due to AAS administration,[59,145,152,154,164,165] although in one study an elevation of approximately 23%[151] has been observed. The aberrant result of the latter study is hard to explain since in other studies of this Finnish research group with the same strength athletes as volunteers no effect on triglycerides were reported.[152]

Apolipoproteins

Only a few studies have investigated the effects of AAS on apolipoproteins in healthy young athletes. These studies mainly focused on serum apolipoproteins A-1 and B levels. They demonstrated that AAS diminish serum apolipoprotein A-1 levels[143,154,165,171] and induce elevations of apolipoprotein B levels.[154,165,171] However, nandrolone decanoate does not seem to affect the apolipoproteins at all.[154] These findings are not surprising since apolipoproteins are very closely related to HDL- and LDL-cholesterol and are in accordance with results in non exercising humans.[173,177,178] However, the magnitude of changes may depend on the drug and dose administered.[174] The 17-α-alkylated drugs (e.g. stanozolol) rather than testosterone esters are responsible for inducing more profound effects.[143,165,174] The same holds true for polydrug regimens when compared with single-drug use.[154] The time course until complete recovery of serum apolipoproteins after drug withdrawal depends on the duration of the AAS course used.[154]

Lipoprotein(a)

Recently, lipoprotein(a) [Lp(a)] has been recognised as an independent risk factor for cardiovascular disease. The fat composition of Lp(a) is comparable with that of LDL-cholesterol accompanied by the presence of a specific apoprotein(a). The serum levels of Lp(a) seem to be genetically determined and, when elevated, can be hardly influenced by nutrition and drugs. However, AAS have been demonstrated to improve serum Lp(a) levels in men and women.[176,179] Research in AAS-abusing ath-

letes has been started very recently and, therefore, only few data are available. In a cross-sectional study, Cohen et al.[180] were the first researchers to observe that AAS-using bodybuilders possessed beneficial serum Lp(a) levels, while non-using bodybuilders showed atherogenic Lp(a) levels.[180] In a series of prospective (blinded and unblinded) studies Hartgens and coworkers[154] demonstrated a strong Lp(a)-lowering effect of polydrug regimens of AAS in strength athletes, while the effect of administration of intramuscular nandrolone decanoate 200 mg/week for 8 weeks was nonsignificant. More research is warranted to elucidate the effects on Lp(a), and the impact of unfavourable changes of serum lipids and lipoprotein levels in combination with a beneficially altered serum Lp(a) level.

Summary on Lipids and Lipoproteins

In summary, many studies investigating therapeutic and supratherapeutic doses of AAS administration have consistently demonstrated that serum lipids and lipoproteins are unfavourably altered by these substances. However, the effects may vary considerably with regimen and types of AAS used, and with route of administration. Serum total cholesterol and triglyceride levels seem to remain unaffected by AAS abuse. Several AAS have been demonstrated to suppress serum HDL-cholesterol levels, with a more distinct effect on HDL2- rather than on HDL3-cholesterol. LDL levels will increase and parallels the pattern of HDL-cholesterol suppression. The effects on apolipoprotein A and B-1 are in line with the effects on HDL- and LDL-cholesterol, resulting in AAS-induced elevations of apolipoprotein A and a decline of apolipoprotein B-1. Recent research indicated that Lp(a) levels may be beneficially affected by the administration of a combination of several AAS in high doses.

The unfavourable effects of alkylated AAS exceed those of testosterone esters. The influence of polydrug regimens on lipoprotein metabolism is more pronounced than the administration of a single steroid. Moreover, short-term administration of nandrolone decanoate, even at high doses, does not affect lipoprotein metabolism in young athletes. On the other hand, long-term use of nandrolone decanoate in patients alters lipoprotein levels considerably.

The sometimes dramatic changes in serum lipids and lipoprotein levels exposes the AAS user to an increased cardiovascular risk, although the impact of short-term disturbances of the cardiovascular risk profile in otherwise healthy young athlete is unknown yet. This ignorance is enhanced by the possible beneficial alteration of Lp(a) levels. Disturbed serum lipids and lipoproteins may recover within a few months, although this is strongly dependent on duration of the AAS course rather than on the dosages used.

4.3.3 Heart Structure and Function

The introduction of echocardiography was important for investigating the physiological responses of the heart to exercise and training. Echocardiography has also been applied for evaluation of AAS on heart structure and function. Eight cross-sectional studies observed differences in one or more echocardiographic variables between AAS users and non-using strength athletes,[33,34,147,181-185] whereas five studies did not register any difference[146,171,186-188] (table V). Compared with non-users, steroid users have been demonstrated to show larger left ventricular mass and/or left ventricular index,[34,147,181-185] and larger posterior wall and interventricular septum thicknesses.[33,34,147,183,184] The majority of studies seem to show that the left ventricular cavity during diastole and systole is not subject to alterations under the use of steroids.[146,171,182,184-187]

To date, only six prospective echocardiographic studies have been published[34,144,171,182,186,188] (table VI) and only one study reported steroid-induced changes in echocardiographic variables.[34] Sachtleben et al.[34] observed significant changes of left ventricular mass, interventricular septum thickness and left ventricular end-diastolic diameter, but the left ventricular posterior wall thickness remained unaffected by AAS.[34] However, the researchers did not pay attention to an increase in work load of the AAS users during the study period. Therefore, these results must be interpreted with caution, especially since all other studies unanimously reported no

Table V. Cross-sectional echocardiographic studies investigating the effects of androgenic-anabolic steroids (AAS) on cardiac structure and function (empty cells indicate 'not measured')

Cross-sectional studies (year)	Subjects	LA (mm)	LVEDD (mm)	LVESD (mm)	IVS (mm)	LVPWT (mm)	LVEDV (mL)	LVM (g)	LVMI (g/m²)	VF (%)	RVEDD (mm)	E/A
Salke et al.[187] (1985)	Bodybuilding		o	o	o	o				o		
Zuliani et al.[171] (1988)	Bodybuilding		o	o	o	o				o	o	o
McKillop et al.[184] (1989)	Bodybuilding		o		o	+	o	+				
Urhausen et al.[33] (1989)	Bodybuilding	o	o	o	+	+	+	o		o		
Climstein et al.[181] (1990)	Powerlifting							+				
De Piccoli et al.[182] (1991)	Bodybuilding	o	o		o	o	o	+	+			
Spataro et al.[188] (1992)	Bodybuilding		o						o			
Thompson et al.[146] (1992)	Weightlifters	o	o	o	o	o		o		o		
Sachtleben et al.[34] (1993)	Bodybuilding		+		+	+		+				
Palatini et al.[186] (1996)	Bodybuilding		o	o	o				o	o		o
Dickerman et al.[128] (1996)	Bodybuilding		o	o	+	+				o		o
Yeater et al.[185] (1996)	Weightlifters	o	o		o	o		+	+			
Di Bello et al.[189] (1999)	Weightlifters		o		o	o		+	+	o		
Karila et al.[147] (2003)	Power athletes		+		+	+		+	+			o

E/A = ratio of E-top/A-top; **IVS** = interventricular septum diameter; **LA** = left atrium diameter; **LVEDD** = left ventricular end diastolic diameter; **LVEDV** = left ventricular end diastolic volume; **LVESD** = left ventricular end systolic diameter; **LVM** = left ventricular mass; **LVMI** = left ventricular mass index; **LVPWT** = left ventricular posterior wall thickness; **RVEDD** = right ventricular end diastolic diameter; **VF** = ventricular fractional shortening; **+** indicates increase of parameter; **o** indicates no effect on parameter.

changes in any echocardiographic variable measured during AAS administration.[144,171,182,186,188] Although a nonblinded design was applied in all studies except one,[144] these results indicate that changes in heart structure and function are not to be expected when an athlete takes AAS for periods of up to 4 months.[144] The effects of prolonged AAS abuse and/or the use of many successive AAS courses remain unknown. Nevertheless, animal studies clearly have shown that short-term use of androgens and anabolic agents may exert strong hazardous effects on cardiac structure and function[190-202] and, therefore, it has been proposed that echocardiography might be not sensitive enough to detect early and small changes due to AAS administration.[144]

4.4 Hepatic Effects

Liver function disturbances and diseases due to AAS treatment in patients, as well as in AAS-abusing athletes, have been of great concern since animal studies have clearly shown the hazardous effects of AAS on the liver.[203,204] Taking into account the results of the trials, it is plausible that AAS can induce serious liver disorders such as subcellular changes of hepatocytes, impaired excretion function, cholestasis, peliosis hepatis and hepatocellular hyperplasia, and carcinomas in humans.[7,9,205-207] Additionally, several case reports have associated the occurrence of aforementioned liver disorders with the abuse of AAS in young, healthy athletes.[208-211] These disease conditions are mainly attributed to the administration of 17-α-alkylated steroids, that is, methyltestosterone, oxymetholone, fluoxymesterone, norethandrolone and metandienone.[7,9,13,206] Injectable testosterone cipionate and enantate preparations do not appear to affect liver function enzymes, whereas (nor-)testosterone esters may induce parenchymal lesions of the liver.[9] Some researchers have proposed that the occurrence of AAS-induced liver disease may be dependent on the liver condition before starting drug administration.[7,13]

Several studies have investigated the effects on serum liver enzyme activities in athletes. In most

Table VI. Longitudinal echocardiographic studies investigating the effects of androgenic-anabolic steroids (AAS) on cardiac structure and function (empty cells indicate 'not measured')

Longitudinal studies (year)	Subjects	LA (mm)	LVEDD (mm)	LVESD (mm)	IVS (mm)	LVPWT (mm)	LVEDV (mL)	LVM (g)	LVMI (g/m²)	RVEDD (mm)	E/A	Remarks
Zuliani et al.[171] (1989)	Bodybuilding		o	o	o	o				o		1 subject used HGH also
De Piccoli et al.[182] (1991)	Bodybuilding	o	o	o	o	o	o	o	o			
Spataro et al.[188] (1992)	Bodybuilding		o						o			
Sachtleben et al.[34] (1993)	Bodybuilding		+		+	o		+				
Palatini et al.[186] (1996)	Bodybuilding		o	o	o				o		o	
Hartgens et al.[144] (2003)	Bodybuilding	o	o	o	o	o		o	o	o	o	

E/A = ratio of E-top/A-top; **HGH** = human growth hormone; **IVS** = interventricular septum diameter; **LA** = left atrium diameter; **LVEDD** = left ventricular end diastolic diameter; **LVEDV** = left ventricular end diastolic volume; **LVESD** = left ventricular end systolic diameter; **LVM** = left ventricular mass; **LVMI** = left ventricular mass index; **LVPWT** = left ventricular posterior wall thickness; **RVEDD** = right ventricular end diastolic diameter; **+** indicates increase of parameter; **o** indicates no effect on parameter.

studies, the common liver enzymes ASAT, alanine aminotransferase (ALAT), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH) and alkaline phosphatase (AP) were studied. Monitoring of liver function enzymes during AAS administration provided equivocal results. However, the majority of longitudinal studies reported no changes due to AAS,[43,53,58,59,62,63,65,96,212] although elevations of ASAT or ALAT have been observed within several weeks of taking steroids in some studies.[48,56,148,213] These elevations were attributed to the intake of oral steroids and tended to return to baseline levels within several weeks after cessation.[48,96] On the other hand, serum levels of GGT, AP and LDH remained unaffected in all studies.[59,62,63,96,148,214] Recently, Dickerman et al.[214] stated that elevations of serum aminotransferase levels may represent muscle damage rather than hepatic dysfunction because of the close relationship to increments of serum CK levels. They demonstrated that GGT was the most distinctive enzyme for the detection of hepatic dysfunction in exercising volunteers. Therefore, the authors recommended evaluation of hepatic function in AAS users to determine CK and GGT levels in addition to ASAT and ALAT.[214]

4.5 Psyche and Behaviour

4.5.1 The Relationship between Serum Testosterone Levels and Mental State/Behaviour

When AAS abuse by athletes first began the medical society (and others) were rightly concerned about the untoward physical effects. Later it became obvious that these agents exert profound effects on psyche and behaviour. From animal and human studies the relationship between endogenous male sex hormones on one side and psychological function and/or behaviour on the other has been assessed thoroughly. In several animal species a relationship between endogenous testosterone levels and aggressive behaviour was likely to be present; however, the findings in humans were less consistent.[215] From clinical studies it appeared that aggressive behaviour and endogenous testosterone levels did not correlate very well.[22,216]

4.5.2 Case Reports

The first observations of psychological function alterations due to AAS abuse were reported in case studies describing athletes abusing huge amounts of such steroids.[217-220] For example, self-administration of AAS was associated with the occurrence of schizophrenia,[217] steroid dependence,[218] affective and psychotic symptoms,[219] and homicide and near-homicide.[220] Moreover, many other changes of mental health and behaviour due to AAS abuse have been reported in the literature,[215,221,222] including hypomanic episodes,[223] violent murder,[224] child abuse[223,225] and spouse battery.[225]

4.5.3 Aggression and Hostility

One of the first reports investigating the effects of AAS on psyche and behaviour in athletes was performed by Lindstrom et al.[226] In their survey, male bodybuilders reported mood changes and an increased libido when on steroids.[226] Many articles have been published since then; self-reporting of athletes as well as survey studies indicate that AAS users seem to be subject to an increase of aggression and/or hostility.[35,227-237] Conversely, some investigations did not observe such a relationship[77,238] and in one study strength athletes were found to demonstrate even lower hostility with anabolic steroids.[239]

4.5.4 Mood

Some researchers could not demonstrate any effects on mood while others observed mood disturbances in AAS users, although the alterations may be very subtle sometimes.[77,226,233,234,236,237,240-242] Mood changes associated with AAS abuse included depression,[234-236,241] paranoia,[235] (hypo)-mania[236,237] and psychotic features.[235] Some studies indicated that the occurrence and seriousness of mood disturbances are dose dependent,[236,237,243] and the effect may be not uniform across individuals since only few individuals will be affected; most will show only little psychological alterations while only a few may develop prominent changes.[243]

4.5.5 Body Image

The relationship between body image and AAS use was subject of a small number of studies. These investigations demonstrated that AAS users are often dissatisfied with their body and have low self-esteem.[244] This may lead to the so-called 'reverse anorexia syndrome'[241,245,246] that was later defined as 'muscle dysmorphia' as an expression of a form of body dysmorphic disorder. This syndrome refers to athletes (in general, bodybuilders, although it may refer to others as well) who believe they have a small and disproportionate body and are pathologically preoccupied with their degree of muscularity.[247] Because of their pathological preoccupation, these subjects have been suggested to be more susceptible to taking AAS.[241,245] Furthermore, AAS-using bodybuilders and weightlifters were found to possess a more narcissistic personality compared with non-users.[221] Recently, Pope and Katz[248] introduced the term 'Adonis complex' for athletes who experience such personality changes.

4.5.6 Dependence and Withdrawal Effects

During the last decade, AAS dependence and the withdrawal effects of AAS have been subject to research. In 1989, Kashkin and Kleber[249] proposed the anabolic steroid addiction hypothesis and suggested that a proportion of AAS abusers are prone to developing addictive disorders, although their hypothesis was not proven at that time. Shortly thereafter, several investigations exploring the relationship between AAS abuse and mental disorders appeared in the scientific literature. Brower et al.[250] reported that more than half of the AAS users demonstrated symptoms consistent with a diagnosis of dependence.[250] However, more recent research could not confirm such a high percentage of addictive AAS users, instead reporting that AAS dependence may exist in approximately 25% of users.[236,238,251] Risk factors for dependency on AAS involve a perception of oneself as not being big or strong enough and long-term abuse of high doses of AAS.[252] On the other hand, withdrawal effects seem to occur in only a small number of AAS users.[219,241,251,252]

4.5.7 Female Athletes

The psychological effects of illicit AAS use in women have seldom been studied. In two studies, female athletes reported an increase in aggressiveness when on steroids.[105,253] Gruber and Pope[254] assessed the psychiatric status of female athletes

attending gyms. Of these women, one-third had a history of AAS abuse. The researchers observed a number of mental abnormalities among AAS users, including polysubstance dependence, hypomanic symptoms, depressive symptoms during withdrawal, rigid dietary practices, non-traditional sex roles and chronic dissatisfaction and preoccupation with their physiques ('muscle dysmorphia').[254]

4.5.8 Summary

Summarising the literature, it can be concluded that AAS may exert profound effects on mental state and behaviour, although only a small number of abusers may be affected. Increased aggression and hostility seem the most prominent alterations observed, although this condition may become serious in only a limited number of users. Mood disturbances may occur, the extent of which is dose dependent. AAS users often expose a narcissistic personality and are often dissatisfied with their own body. Pope and Katz[248] introduced the concept that subjects with these characteristics suffer from the Adonis complex, referring to a mythological character with the same personality traits. Furthermore, an individual's dissatisfaction with their body is a risk factor for developing AAS dependence, as is the abuse of these substances for longer periods in supratherapeutic doses.

4.6 Other Adverse Effects

AAS abuse has been proven to have the potential to dramatically disturb the hypothalamic-pituitary-gonadal axis, although other endocrine systems have also been shown to be susceptible for these substances. Deregulation of glucose metabolism secondary to insulin resistance[255,256] and impairment of thyroid function[114,257] have been observed. Moreover, the effects on skin may be profound. Kiraly and coworkers[155,258,259] found enlargement of sebaceous glands, increase of sebaceous production and elevation of skin surface lipid cholesterol levels due to AAS.[155,258-260] Furthermore, these agents were found to reduce immune function,[261] to affect the haemostatic system[8,262-264] and to alter soft tissue collagen metabolism,[265] although the clinical relevance of these observations is yet to be determined. Recently, Pärssinen et al.[266] reported a 4-fold increase in the mortality rate among powerlifters who were strongly suspected to have used AAS for several years in the past compared with control subjects over a 12-year follow-up period. Suicide and acute myocardial infarction were the most prevalent causes of premature death among the athletes.[266]

In case reports, many other side effects of AAS abuse among athletes have been published. It is inevitable that dramatic side effects may occur in some individuals as a result of the huge amounts of substances administered. In a number of case studies, AAS have been reported to affect the musculoskeletal system by causing bone fractures,[267] tendon pathology[268-271] and rhabdomyolysis.[272-274] In several case studies the development of dermatological adverse effects have been described, including occurrence of acne vulgaris,[275] acne fulminans,[276] hereditary coproporphyria,[277] linear keloid formation[278] and exacerbations of psoriasis.[279] However, whether these reported conditions are adverse effects of AAS or not has yet to be established since, in contrast, AAS are used in experimental clinical trials in the treatment of several dermatological disease conditions.[32] Alterations of the prostate and bladder have also been attributed to these steroids,[280] as have several malignant diseases in young athletes, for example, Wilms' tumour,[281] renal cell carcinoma[282] and carcinoma of the prostate.[283,284] Even very rare disease conditions, such as sleep apnoea syndrome (Pickwick disease), were also linked to AAS administration.[285] Although a large number of reports associated AAS abuse in healthy young athletes with the occurrence of a broad spectrum of (sometimes dramatic) side effects, this may not always reflect a causal relationship with AAS and, therefore, such reports must be interpreted with caution.

5. Mechanism of Action

The mechanism of action of AAS is not completely understood and is still subject to research. Several general mechanisms have been demonstrated to explain action of AAS, while in recent years several specific mechanisms and theoretical models

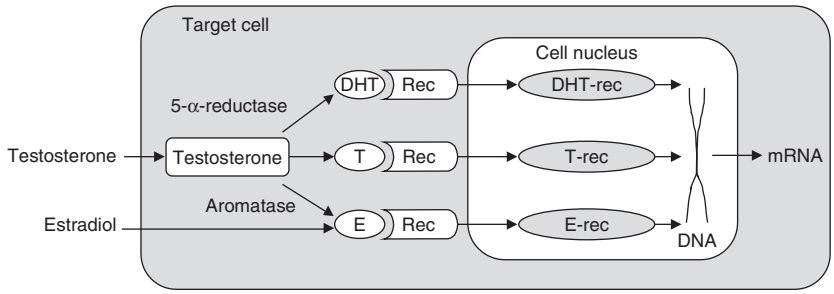

Fig. 1. Mechanism of action of testosterone. **DHT** = dihydrotestosterone; **E** = estradiol; **DHT-rec** = dihydrotestosterone-receptor complex; **E-rec** = estradiol-receptor complex; **Rec** = receptor; **T** = testosterone; **T-rec** = testosterone-receptor complex.

of action on tissue and organs have also been recognised. Figure 1 illustrates the general mechanism of action of AAS.

5.1 General Mechanism

The mechanism of action of AAS may differ between compounds because of variations in the steroid molecules. These variations are responsible for differences in the specificity of binding to receptor proteins or to interaction with various steroid-metabolising enzymes.[13,18,23] With respect to interactions with intracellular steroid receptor proteins, several pathways can be distinguished.[18,286] First, binding with high affinity to androgen receptors – these steroids are therefore recognised as strong androgens (e.g. 19-nortestosterone, metenolone).[286,287] Secondly, several compounds are characterised by binding with low affinity to androgens and therefore are weak androgenic substances (e.g. stanozolol, fluoxymesterone).[286,287] Thirdly, some AAS (e.g. oxymetholone) do not bind to the androgen receptor at all.[286] These steroids are supposed to act after biotransformation to more active compounds or via alternative mechanisms of action. Furthermore, it has been established for AAS that other mechanisms may also be involved.[13,288]

5.2 5-α-Reductase

The enzyme 5-α-reductase has been recognised as playing an important role in the mechanism of action. Figure 1 shows that this enzyme converts AAS into the more active compound dihydrotestosterone.[13] After diffusion into the cells of target tissue, AAS may be subject to two main pathways. The steroid binds directly, or after conversion to the more active compound dihydrotestosterone, to specific receptors for androgens.[287] This results in the formation of a steroid-receptor complex in the cell nucleus. The steroid-receptor complex stimulates the protein synthesis by interaction with RNA and DNA.[17,289]

The most important organ systems with high 5-α-reductase activity are the male accessory sex glands, the skin, the prostate, the lungs, the brain, fat cells and bone. Therefore, these organs posses a high affinity to androgenic rather than to anabolic compounds. Conversely, there are organs (e.g. heart and skeletal muscle) that posses a low 5-α-reductase activity and exert a stronger response to anabolic substances.

5.3 Aromatase

Another enzyme, aromatase, seems to play a limited role under normal circumstances. This enzyme is located inside the cell and is responsible for conversion of AAS into the female sex hormones, such as estradiol and estrone (figure 1). Female sex hormones bind to estrogen receptors and form estrogen-receptor complexes. These complexes exert their effects in fat tissue, Leydig and Sertoli tissue and in some nuclei in the CNS. This mechanism will probably only be activated when the androgen receptor system is saturated by the circulating androgens and anabolic steroids. Conversely, AAS may have an antagonistic action on estrogens when supraphysiological serum levels of AAS are present. This will lead to saturation and down-regulation of

the androgen receptors. The excess of AAS will then try to bind to the estrogen receptors in competition with the estrogens available. Therefore, the net outcome of these two conflicting pathways is not predictable.

5.4 Anti-Glucocorticoid Action

Complementary to the competitive antagonism with the estrogen receptors, a similar competitive antagonism has been described with respect to glucocorticoid receptors.[290] Glucocorticoids are substances with catabolic properties that will be released in the serum as a result of (strong) physical or mental stress, e.g. exercise training, surgery and psychological problems. By binding to the glucocorticoid receptors, the AAS are able to counteract the breakdown of proteins by the glucocorticoids.[291] This competitive antagonism may also play a role in the treatment of osteoporosis through reduction of bone breakdown and stimulation of bone formation. Recently, evidence has become available that AAS stimulate proliferation and differentiation of osteoblastic cells and have the capacity to counteract bone breakdown. Testosterone has also been found to correct calcium balance and bone formation, playing a role in the reduction of bone resorption.

5.5 The Haematological System

AAS are considered to influence the haematological system via two main pathways. First, anabolic steroids stimulate erythropoiesis directly and erythropoietin synthesis in the kidney.[292] Secondly, the effects of androgens have been demonstrated to promote erythropoietic stem cell differentiation and to increase the sensitivity of erythroid progenitors.[293,294] Since the introduction of recombinant human erythropoietin in the 1980s, the administration of AAS for the these effects has been relegated to the background both by clinicians and athletes.

5.6 Muscle

Research by Kadi and coworkers[81,82,86,87] have enhanced insight into the mechanism of action of AAS on muscles. The AAS-induced increase in muscle mass can be attributed to both muscle hypertrophy and the formation of new muscle fibres.[81,87] Kadi et al.[82,86] also hypothesised that the fundamental process for muscle fibre growth appeared to be the incorporation of the satellite cells into preexisting fibres to maintain a constant nucleus to cytoplasm ratio. Moreover, key roles seem to be played by satellite cells, that is, they are enhanced by AAS administration, and androgen receptors. Androgen receptors are expressed in myonuclei of muscle fibres and in capillaries and are more present in neck and shoulder muscles than in limb muscles. AAS administration induces an increase in androgen receptor-containing myonuclei in the shoulder girdle muscles but not in the vastus lateralis,[81,82] although Sinha-Hikim et al.[89] demonstrated that high doses of testosterone were also able to increase the myonuclear number per fibre in the vastus lateralis muscle. Recently, Sinha-Hikim and associates[92] also observed that muscle hypertrophy induced by exogenous testosterone administration was associated with an increase in satellite cell number, changes in satellite cell ultrastructure and a proportionate increase in myonuclear number. These observations may, at least partially, explain the regional differences in body changes and muscle fibre adaptation.[82,85] Moreover, it has been hypothesised that alterations in muscle mass may be explained by action of AAS on the mesenchymal pluripotent cell.[295]

5.7 The Cardiovascular System

The cardiovascular system may be affected via at least four different pathways, as proposed by Melchert and Welder.[10] Although hypothetical, they provide interesting models to explain AAS-induced adverse effects on this system.

5.7.1 The Atherogenesis Model

The atherogenesis model is based on the association between AAS and HTGL, an enzyme that regulates serum lipids and lipoproteins.[173] AAS administration enhances HTGL activity that decreases regression of atherosclerotic plaques by suppression of serum HDL-cholesterol and elevation of LDL-cholesterol.

5.7.2 The Thrombosis Model

The thrombosis model is characterised by influence on the haemostatic system, with the strongest effects of AAS on platelet aggregation that results in enhanced blood-clot formation, including an increased cardiovascular risk.

5.7.3 The Coronary Artery Vasospasm Model

Since no evidence of atherosclerosis or thrombosis of the coronary arteries was involved in several reports of sudden cardiac death, nitric oxide has been suggested to play a role in the third model, the coronary artery vasospasm model. Nitric oxide acts as an endothelial-derived relaxing factor in smooth muscles of arteries. AAS may inhibit nitric oxide properties and may induce vasospasm, although the authors suggested that other models may be involved in conjunction with the vasospasm theory. The latter is supported by recent findings in animal studies.[296,297] Tagarakis et al.[296,297] demonstrated that AAS may impair capillary supply of the heart as a result of an increase in myocardial muscle mass and a relative decrease in capillary density, which may provoke compression of coronary vessels that could trigger myocardial infarction.[296,297]

5.7.4 The Direct Injury Model

The fourth hypothesis proposed by Melchert and Welder[10] is the direct injury model. AAS is hypothesised to induce direct myocardial cell injury, leading to myocardial cell death and replacement of dead cells by scar tissue within the myocardium. Development of fibrotic areas predisposes to arrhythmias, which exposes the individual to an increased risk of fatal events. Postmortem pathological findings in previous AAS users included focal, regional, interstitial and disseminated fibrosis of the myocardium, although the impact of myocardial fibrosis is still unclear.[140-142]

5.7.5 Other Models

Several other hypotheses have been postulated, especially those affecting red blood cells and volume. Recently, Fineschi et al.[139] suggested that cardiac arrest may be mediated catecholamine myotoxicity associated with ventricular fibrillation due to myocardial necrosis and degenerative changes within the intramyocardiac sympathetic neurons.[139]

All mechanisms proposed for explaining cardiovascular disease due to AAS use have interesting points; however, future research is needed to clarify the relevance of each theory.

6. Conclusions and Future Directions

AAS in supratherapeutic doses may increase muscular strength and lean body mass in athletes, whereas endurance performance and fat mass appear to be unaffected. Because of the widespread use of large doses of AAS, the adverse effects are of great concern. The effects on the reproductive system appear to be profound and may lead to libido changes and (temporary) infertility. AAS affect risk factors of cardiovascular disease unfavourably, especially serum lipoprotein profiles. Although the effects on BP and cardiac structure and function are not yet conclusive, AAS may also affect them. Unlike the amounts of AAS used by athletes, the adverse effects on liver function seem to be limited. Recently, it has become apparent that AAS may exert strong effects on psyche and behaviour.

Future research should primarily focus on the short- and long-term effects of intermittent AAS abuse on health, the effects on health after AAS withdrawal, as well as on the long-term health effects in recalcitrant AAS users. Investigating the alterations of the reproductive and cardiovascular systems, as well as psyche and behaviour alterations, should have highest priority.

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Correspondence and offprints: Dr *Fred Hartgens*, Department of Surgery, Outpatient Clinic Sports Medicine, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands.
E-mail: fhartgens@home.nl